APPLES TO APPLES: THE ORIGIN AND MAGNITUDE OF DIFFERENCES IN ASBESTOS CANCER RISK ESTIMATES DERIVED USING VARYING PROTOCOLS

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ABSTRACT

Given that new protocols for assessing asbestos-related cancer risk have recently been published, questions arise concerning how they compare to the "IRIS" protocol currently used by regulators. The newest protocols incorporate findings from 20 additional years of literature. Thus, differences between the IRIS and newer Berman and Crump protocols are examined to evaluate whether these protocols can be reconciled. Risks estimated by applying these protocols to real exposure data from both laboratory and field studies are also compared to assess the relative health protectiveness of each protocol. The reliability of risks estimated using the two protocols are compared by evaluating the degree with which each potentially reproduces the known epidemiology-study risks.

Results indicate that the IRIS and Berman and Crump protocols can be reconciled; while environment-specific variation within fiber type is apparently due primarily to size effects (not addressed by IRIS) the 10-fold (average) difference between amphibole asbestos risks estimated using each protocol is attributable to an arbitrary selection of the lowest of available mesothelioma potency factors in the IRIS protocol. Thus, the IRIS protocol may substantially underestimate risk when exposure is primarily to amphibole asbestos. Moreover, while the Berman and Crump protocol is more reliable than the IRIS protocol overall (especially for predicting amphibole risk), evidence is presented suggesting a new fiber size-related adjustment to the Berman and Crump protocol may ultimately succeed in reconciling the entire epidemiology database. However, additional data need to be developed before the performance of the adjusted protocol can be fully validated.

1. INTRODUCTION

Given that new protocols for assessing asbestos-related cancer risk have been published in recent years[1-4], questions inevitably arise concerning how they compare to each other and to the "IRIS" protocol[5] in current use by regulators. The approach in IRIS was developed based on an analysis presented almost 25 years ago in the EPA Health Effects Assessment Update[6], henceforth referred to here as the 1986 Update. Much literature addressing asbestos carcinogenicity has been published in the interim and has been the subject of various reviews[3,4,7,8] and the more recent protocols incorporate results from the latest epidemiology studies.

It is of interest both to quantify differences in the magnitudes of risk estimated using the various protocols and to identify the origin of any significant differences that are found. Among other things, the latter typically indicates how the various protocols can be reconciled.

Of the available protocols, those of IRIS[5] and Berman and Crump[2-4] are closely related. Both rely on similar models to estimate lung cancer and mesothelioma potency factors (K_L's and K_M's) from published studies of occupationally exposed cohorts covering diverse exposure environments. Both then input selected K_L's and K_M's into a lifetable analysis to derive excess lifetime risk estimates for asbestos-related cancers. These are suitable for predicting risk in new environments and can be converted into unit risk factors (URFs) that facilitate their application. Typically, risks are then estimated simply as the product of a mean (lifetime, continuous) exposure concentration and a properly matched URF from the appropriate protocol.

The Berman and Crump protocol differs from that of IRIS by incorporating (1) an additional parameter in the lung cancer model to address mismatches between background lung cancer rates among cases and referents; (2) epidemiology studies with more recent follow-up that also cover a more diverse range of exposure environments than those available in 1986; (3) more recent data in the lifetable analysis that describe background mortality, smoking frequency, and contributions by smoking to background lung cancer rates in the general population; (4) a different approach for converting between occupational and lifetime, continuous exposure scenarios; and, perhaps most important, (5) a different procedure for selecting the K_L's and K_M's that were used for the lifetable analysis.

For the IRIS protocol, the lowest K_M (1.0×10^{-8}) and a midrange K_L (0.01) were arbitrarily selected for use from among available, published values. Also, the decision to apply these values to both chrysotile and amphibole asbestos was suggested solely by an informal model[1] for estimating K_M/K_L ratios. In contrast, Berman and Crump fit a model incorporating factors reflecting fiber[2] size and mineral type to the distribution of K_L's and, separately, K_M's derived from the published epidemiology studies. Upper bound estimates of the K_L and K_M values derived from the fits of their model were then employed in their lifetable analyses.

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1 This model is informal because it was neither fit to data nor was the agreement between model results and measured values statistically evaluated in any other manner.

2 As used here and throughout, the term "fiber" includes not only single fibers (fibrils), but the bundles, clusters, and matrices that make up the set of fibrous particles found in an asbestos dust[9].

Fitting the K_L's and K_M's to models addressing fiber size allows optimization of the exposure metric[3] used to assess risk in addition to the potency factors used to develop the corresponding URFs. Berman and Crump[2-4] have shown that considering size improves the agreement between risks predicted using a protocol and the dispirit risks observed across the published epidemiology studies. The ultimate goal of their work is to find the metric that best reflects carcinogenicity, which should reconcile differences in predicted and observed risks.

The objective of this paper is to explain (reconcile) the differences in risks estimated, respectively, using the IRIS and the Berman and Crump protocols. In contrast, variation in risks estimated across different versions of the Berman and Crump protocol[2-4] (to the extent they are due to fiber size) indicate an improving ability to identify the metric that best reflects asbestos carcinogenicity. Thus, the reason for these differences is already known (reconciled).

Results of applying the IRIS and Berman and Crump protocols to actual dusts either generated in a controlled, laboratory environment or observed in outside air (at sites where asbestos exposure is an issue of concern) are also compared to evaluate the relative health protectiveness[4] afforded by the various protocols. The reliability of each protocol is also evaluated by assessing how well each reproduces the known risks reported in the published epidemiology studies.

Because the protocol by Hodgson and Darnton[1] involves use of models that differ in structure from those employed by both IRIS and Berman and Crump, the evaluation presented in this study is not adequate for reconciling Hodgson and Darnton with these approaches. Therefore, detailed consideration of the Hodgson and Darnton protocol will be addressed in a separate study. Nevertheless,. as previously indicated[4], the findings of Hodgson and Darnton are not inconsistent with those of Berman and Crump.

2. BACKGROUND

Asbestos dusts are complex mixtures of fibers of varying sizes and (sometimes) mineral types. Analytical methods used to determine asbestos concentrations typically contain language defining a subset range of fiber sizes (a metric) that are counted to determine concentrations in the dusts. Fibers counted using different methods may also differ due to limitations in the ability to observe them; this is a function of the type of microscope used for analysis. These latter two factors mean that asbestos concentrations determined in any particular environment may differ by orders of magnitude depending on the specific analytical method employed during analysis[3,10-Chapter 4].

The protocols considered in this study are linked to different analytical methods and, consequently, to different metrics. Thus, to develop exposure concentrations suitable for assessing risk using a particular protocol requires counting asbestos fibers that satisfy the definition of the same metric as that of the

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3 An exposure metric is the specific size range of fibers that are counted during analysis to determine exposure concentrations.

4 As used here, a risk estimate is health protective if it is unlikely to be smaller than the true risk it represents. Correspondingly, a protocol is health protective if it is unlikely to yield underestimates of true risk. Thus, by this definition, larger risk estimates are more health protective than smaller risk estimates representing the same true risk.

protocol; protocols should only be applied to exposure concentrations determined for the corresponding metric[5].

Due to complex history and evolving technology, varying metrics were applied for determination of exposure concentrations in the available epidemiology studies[e.g., 11]. Among published studies, although a variety of methods were initially employed, most were ultimately determined by a method based on phase contrast microscopy (PCM)[12],[6]. The corresponding PCM metric includes counts of "fibers" that are defined as particles longer than 5 μm with an aspect (length to width) ratio ≥ 3 and largely parallel sides. They must also be visible when viewed by PCM at a magnification of 400X[19,20].

Due to the limitations of PCM, the mineral type of fiber cannot be determined[21,22] and only fibers thicker than approximately 0.15-0.4 μm, depending on mineral type, are included in these counts[23-25]. In fact, the minimum width of fibers visible by PCM is controversial. NIOSH[22] defines this minimum width as 0.25 μm and use of this width has generally resulted in good agreement between PCM counts and counts by transmission electron microscopy (TEM) that are intended to mirror the same size range[e.g., 26,27]. Thus the NIOSH-defined PCM-equivalent metric (N-PCME metric) for TEM includes counts of fibers longer than 5 μm and thicker than 0.25 μm that exhibit aspect ratios greater than 3.

In contrast, IRIS[5] defines the minimum width for the PCME metric as 0.4 μm. However, the reasons for this distinction are not entirely clear. Not only do laboratories report good agreement between PCM and PCME, when the NIOSH definition is employed, but at least one study[18] suggests that when differences occur, they point in a direction opposite to any "correction" potentially afforded by the IRIS definition. When differences were observed in that study, PCM counts were greater than N-PCME counts (not smaller, as I-PCME counts would necessarily be). This may be why the latest asbestos guidance from the EPA[28] now recommends use of the N-PCME metric at Superfund Sites, although the value in IRIS (which requires science advisory board review) has not been changed. Importantly, the IRIS protocol has been applied at various times to both the N-PCME and I-PCME metrics so that both applications are considered in this study[7].

The Berman and Crump protocol has been evolving over the years as a broader set of epidemiology (and related) studies become available to better identify an optimum metric for predicting asbestos carcinogenicity. Thus, there have been changes over time to the definition of the metric to which the

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5 While fibers outside the size-range defined for a particular metric are assigned zero potency by default (because they are not counted during analysis), this does not mean that they are in actuality non-potent. It means only that their contributions to the disease-inducing dusts of the original epidemiology studies were assumed[5,6] or shown[2-4] to be adequately addressed by the fibers counted using the selected metric.

6 Recently, two epidemiology studies have provided exposure characterizations based on detailed size distributions developed by TEM[13-17] and inferences from at least the first of these have been addressed with regard to the development of risk protocols[4,18]. Such considerations, however, are beyond the scope of the current analysis.

7 Both PCME metrics typically restrict fibers that are counted only to those that are confirmed to be composed of an "asbestos-related" mineral. Unlike asbestos-related occupational settings (where the majority of fibers can generally be assumed to be asbestos) the IRIS protocol is often applied in environments where other types of fibers may be present. Thus, these restrictions are designed to exclude organic or other fibers not believed to contribute to asbestos-related disease and TEM is capable of distinguishing such characteristics. While details concerning what constitutes an asbestos-related mineral are controversial[e.g., 3,4,7,28], such considerations are addressed only briefly in the current study.

protocol is linked. Consequently, the following metrics, which must be determined by TEM, are each considered in this study:

- from 2001[2]: protocol structures are those thinner than 0.5 μm and longer than 5 μm with those longer than 10 μm weighted more heavily; fibers between 5 and 10 μm in length are considered to be only 3/1000 times as potent as those longer than 10 μm: protocol structures = $0.003C_{5<L<10} + 0.997C_{10<L}$ (all with width < 0.5 μm);

- from 2003[3]: long protocol structures are those thinner than 0.4 μm and longer than 10 μm. Note that the already small contributions of fibers between 5 and 10 μm in length (in the 2001 protocol) were ultimately found to be unimportant;

- from 2008[4], a second metric (incorporating all widths up to 3 μm) was added to complement the metric originally defined in 2003 because it was shown that the existing epidemiology dataset is not sufficiently diverse to adequately evaluate the effect of width. Thus, the "long protocol structure" metric from 2003 is now renamed the "thin" metric and the new metric is termed the "all-widths" metric.

Note that the justification for each of the above-indicated changes is fully documented in each of the corresponding versions of the protocol, but their consideration is beyond the scope of the current discussion.

Despite these changes, as illustrated in the current study, risk estimates derived by applying the various versions of the Berman and Crump protocol (with their corresponding metrics) have so far remained consistent over time, with one reconciled exception. Future modifications are not expected to remain consistent because, as the effects of fiber size are better addressed, risk estimates for specific environments will necessarily change. This should ultimately allow risks predicted using the Berman and Crump protocol to fully reproduce the risks observed across published epidemiology studies. In fact, although not fully investigated (because adequate data are not yet available to support it) very recent work[18] suggests that one further modification to the protocol may finally reconcile all of the existing epidemiology. The candidate metric identified in 2010[18] includes all fibers longer than 20 μm and widths less than 1.5 μm (with the range of widths remaining to be finalized). The implications of this candidate metric are addressed in this study.

3. MATERIALS AND METHODS

3.1. Unit Risk Factors

Unit risk factors (URFs) were derived from each of the protocols evaluated in this study by:

1. calculating the additional risk of death from lung cancer and mesothelioma associated with a defined reference exposure level;
2. combining the risks from lung cancer and mesothelioma; and
3. dividing the combined risk by the corresponding reference exposure level.

The additional risks of death from lung cancer and mesothelioma were respectively calculated from K_L's and K_M's using a lifetable analysis in the manner previously described[3, Appendix E]. Except for differences in the mortality and smoking data used in these calculations, they are similar to those reported in the 1986 Update[6]. Therefore, to promote comparison, URFs were also derived from the K_L's and K_M's

recommended in the various protocols, but holding constant all other inputs to the lifetable analyses. Calculations were performed using a software package[29] developed to implement the lifetable analysis, which was modified for this study to allow implementation of the other protocols.

3.2. Comparing Protocols Linked to Different Exposure Metrics

As previously indicated, excess risk derived using a particular protocol can be estimated as the product of a URF and an exposure concentration for an appropriately matched exposure metric:

$$Risk_{ij} = C_{ij} * URF_i$$

Thus, the estimated risk (derived based on exposure metric "i") in a particular environment "j" is equal to the product of the mean (lifetime) exposure intensity of fibers satisfying the definition of metric "i" in that environment and the corresponding URF derived for metric "i". As each $Risk_{ij}$ is intended to reflect the rate of disease that ultimately develops in environment "j", estimates of risk developed using different protocols (and their corresponding metrics) are directly comparable. This does not mean, however, that risk estimates derived using a particular protocol are either reliable or even health protective.

Whether risk estimates derived using a particular protocol are reliable can only be judged by comparing such risks to actual disease outcomes. Therefore, one way to evaluate the reliability of a particular protocol is to determine the degree with which it reproduces (fits) the rates of disease observed among the published epidemiology studies. It is also important that the set of epidemiology studies employed to evaluate reliability be sufficiently diverse to cover environments exhibiting the full range of exposure characteristics over which the protocol is intended to be applied.

Whether one protocol is more health protective than another can be evaluated by comparing the magnitudes of the risks estimated by each protocol over the same set of environments. Thus, this is a simpler test than evaluating reliability, but may at least suggest whether human health is being adequately protected when a particular protocol is applied. At the same time, this test cannot identify when risks are being overestimated.

3.3. Risk Estimates

3.3.1. *Sources of data*

Two sources of exposure data were employed in this study. The first involves exposures associated with the dusts studied in the set of animal inhalation experiments reported by Davis and coworkers[30-37], which were reevaluated in a 1995 meta-analysis[38],[8]. As some of the materials employed in these studies were used in actual commerce and others represent modified materials designed to evaluate the effects of fiber size, dusts generated from these materials exhibit diverse characteristics. Note that, as characterizations of these dusts (which were regenerated to support the 1995 meta analysis) have not previously been published, summary tables are provided in an Appendix.

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[8] Additional UICC samples, which were generated to support general asbestos research[39-43] were also characterized in support of the 1995 study[38] and results are also presented in the Appendix to this paper. However, not all of these samples were studied by Davis et al. and those lacking data on disease outcomes could not be included in the 1995 meta analysis.

The second set of data used to evaluate risk protocols are those describing dusts encountered at actual sites studied by regulators. In general, sites were included if the available data are sufficient to estimate risk using at least two of the metrics considered here. Thus, data from the Diamond XX site in California[44]; the former Johns-Mansville manufacturing site in Waukegan, IL[45]; the Southdown Quarry in Sparta, NJ[46]; the Mine in Libby, MT[47]; the site in Klamath Falls, OR[48,49]; and the school yard studied in El Dorado County, CA[50] are each presented.

Importantly, because it is sufficient to evaluate risk ratios when comparing risk protocols, these can be estimated as the product of URF ratios and ratios of either the concentrations or, simply, the fractions (of total fibers) observed for corresponding exposure metrics among the samples of dusts available for this study; it is not necessary to determine absolute exposure concentrations.

3.3.2. *Estimating risk*

Multiplying either the ratio of concentrations or relative fractions by the ratio of corresponding URFs provides the same ratio estimate of risks.

3.4. Fitting the Nicholson Model for K_M/K_L

A quick test of the validity of conclusions drawn from the informal model used to estimate K_M/K_L ratios in the 1986 update[6] was performed by fitting the predictions of this model to currently available, study-specific K_M's. This was done using a modification of the approach described by Berman and Crump[4] for evaluating the effects of fiber size and mineral type. In that approach, the following equation was fit to study-specific K_M's:

$$K_{Mj} = \frac{K_A^* * (f_{Lj} + rps * f_{sj}) * [f_{Aj} + rpc(1 - f_{Aj})]}{f_{pcmej}} \quad (1)$$

For this application, Equation 1 was modified by multiplying both the numerator and denominator of the right-hand side by K_{infj}:

$$K_{Mj} = \left(\frac{K_A^*}{K_{infj}}\right) * \frac{K_{infj} * (f_{Lj} + rps * f_{sj}) * [f_{Aj} + rpc(1 - f_{Aj})]}{f_{pcmej}} \quad (2)$$

K_{infj} is an estimate of K_M derived for a particular study j by multiplying the ratio K_M/K_L (estimated using the informal model from the 1986 update) by K_{Lj} from the same study; and all of the other symbols in the equation retain the same meaning as in Berman and Crump. Thus: K_{Mj} is the study-specific K_M for study j; K^*_A is the mesothelioma potency for pure, long amphibole; rps is the relative potency of a long (vs. a short) size category; rpc is the relative potency of chrysotile and amphibole asbestos; and f_{lj}, f_{sj}, and f_{pcmej} are the fractions of the selected long-, short-, and PCME-sized categories in the fiber size distributions relevant to each environment j, respectively. Note, for reasons described above and in Berman and Crump[4], f_{pcmej} is best represented by the N-PCME metric.

Considering that the K_{infj}'s that are estimated using the informal model are derived from environments in which amphiboles contribute substantially to exposure (so that they can be considered to be rough estimates of K^*_A), the ratio in parentheses to the immediate right of the equal sign in Equation 2 can be considered to be a parameter, Q, indicating how well the K_{infj} actually estimate K^*_A. Ideally, this ratio should exhibit a value of one.

Equation 2 was fit to the study-specific K_M's for cohorts from which K_{inf_j}'s were estimated in the 1986 update[6] to derive estimates of Q, rps, and rpc[9]. The equation was fit considering the PCME size metric (as the model was originally intended) as well as considering the thin and all-widths metrics evaluated by Berman and Crump in 2008[4]. Fits were also conducted holding Q fixed at one.

4. RESULTS

4.1. Origin of Differences

Table I presents a summary of the K_L's and K_M's reported respectively in the 1986 Update[6] and Berman and Crump[7] for each of the epidemiology studies available to the respective authors. The general industry type and specific cohort studied are listed on the left side of the table and the potency factors are grouped into those derived from predominantly chrysotile, mixed, or predominantly amphibole asbestos exposures. Because the Berman and Crump study was conducted more than 20 years after the 1986 Update, studies of a number of additional environments were included in their data set that had not been published in time for inclusion in the 1986 Update.

As can be seen in Table I, the K_L's estimated by Berman and Crump are generally similar to, although slightly smaller than, those reported in the 1986 update. Differences are due both to the consideration of additional data for particular environments (from follow-up studies published after 1986) and incorporation of an additional factor in the lung cancer model by Berman and Crump that accounts for differences in background cancer rates between cases and referents. Considering the uncertainty bounds for each potency factor[4], however, the K_L's reported in both studies are consistent.

It can also be seen from Table I that the K_M's estimated by Berman and Crump are similar to those reported in the 1986 Update and these too are clearly consistent when uncertainty is considered. This is not surprising as the same model was used to assess mesothelioma potency in the 1986[6] and 2008[4] studies. As discussed below, due to limits in the available data, only four K_M's were reported in the 1986 Update and none of these were derived from studies involving predominantly chrysotile exposure. In contrast, Berman and Crump were able to derive 14 K_M's from 12 different environments including four involving predominantly chrysotile exposure.

Table II presents URFs derived from the risk protocols (indicated on the left of the table) using combinations of U.S. mortality statistics, smoking statistics, and factors for converting from occupational to continuous exposure (mortality/smoking scenarios) that are indicated at the top of each column and defined in the corresponding footnote. The table is also divided into URFs intended for chrysotile (on the left) and those intended for amphibole asbestos (on the right).

Going down the table, URFs are grouped under headings indicating the specific exposure metric with which each corresponds. Because concentrations determined for different exposure metrics do not remain proportional from one environment to the next, URFs listed under different exposure metrics cannot be directly compared. Instead, it is only the risks estimated by applying such URFs to corresponding exposures derived from the same environment that can be compared directly to assess

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9 To facilitate calculation, the actual values for the K_M/K_L ratios (and the corresponding K_L's) from Table 3-31 of the 1986 Update[6] were used in this analysis, but the K_M values against which they are compared were derived from Berman and Crump[4]. This means that the K_M's may be based on updates of the original epidemiology studies cited in the 1986 Update. Based on data presented in Berman and Crump, any disparities derived from matching studies in this manner should be small, particularly for the very general purpose to which they are applied here.

the relative health protectiveness of such URFs. In contrast, URFs listed under the same exposure metric (and asbestos type) in the table can be directly compared because they would be multiplied by the same exposure concentration when used to assess risk in a particular environment.

Considering chrysotile and amphibole asbestos separately, differences in the URFs across each column of Table II are attributable to differences in the input statistics or conversion factors (defined in each Mortality/Smoking Scenario) that were employed to derive each value. As can be seen in the table, such differences are small, at most representing changes of about 70% (i.e., < 2x). On the upper right-hand side of the table, for example, it can be seen that the IRIS-recommended URF of 0.23 (for amphiboles) is about 70% of the best estimate (0.35) provided in the 1986 Update[6] (based on Tables 6-1 to 6-3 in the Update). This difference is due to the former being calculated using inputs from Mortality/Smoking Scenario 1 while the latter incorporates inputs from Scenario 2. The IRIS-recommended URF (0.23) is about 75% of the equivalent value (0.31) derived using the inputs of Mortality/Smoking Scenario 4 (which is used below for most comparisons in the table).

Substantially larger differences (more than an order of magnitude) are attributable to choice of the specific potency factors (K_L's and K_M's) used to derive each URF. In the last column of the table (under Mortality/Smoking Scenario 4), for example, it can be seen that the URFs derived for the PCME metric either from use of the maximum K_L and K_M (0.048 and 1.2×10^{-7}, respectively, Table I): URF=2.88 (Table II) or the upper bound value, URF=5.04 (derived by applying the 1986 Update author's uncertainty estimate to his recommended best estimate) are about an order of magnitude larger than the current IRIS value[5], even after adjusting to mortality/smoking scenario 4: URF=0.31.

It should also be noted that no URFs from the 1986 Update are listed for chrysotile in Table II. This is because the data set employed in the 1986 Update lacked even a single estimate for K_M from an environment in which exposure was predominantly to chrysotile. However, values are listed for IRIS, based simply on the assumption that, fiber for fiber, chrysotile and amphibole asbestos are equipotent. This consideration is addressed further below. In contrast, distinct URFs are listed for chrysotile and amphibole asbestos in Table II from those protocols in which a significant difference in the toxicity of these mineral types was reported.

As previously indicated, risks estimated using protocols linked to different metrics are directly comparable, but their URFs are not. Therefore, to judge their relative health protectiveness (and other effects), it is first necessary to apply each protocol to real data, as discussed in the next section.

4.2. Comparing Health Protectiveness

Table III presents normalized risks from dusts analyzed for the 2005 meta-analysis[38]. Risks are normalized to the risk estimated using the IRIS protocol paired with the I-PCME metric for each dust. Prior to normalization, risks were estimated as the product of a URF (selected from Table II) and the fraction of the corresponding exposure metric among fibers of the indicated dust (Appendix Table A-II). With the exception of the URF for PCME (0.23), which is the recommended value in IRIS[5], risks are estimated using the recommended upper bound URF from each protocol, indicated in the right-most

columns of the chrysotile or amphibole section of Table II[10]. Thus, for example, the normalized risk for short chrysotile estimated using the thin metric from Berman and Crump[4] is determined by:

- summing the fraction of short chrysotile fibers in each size category of Table A-II satisfying the dimensions of the 2008[4] thin metric (10 μm < L, w < 0.4 μm), result = 0.029;
- multiplying this value by the recommended (UCB) URF (0.21) for chrysotile fibers of the same metric, result = 0.0061;
- summing the fraction of short chrysotile fibers in each size category of Table A-II satisfying the dimensions for I-PCME, result = 0.023;
- multiplying this value by the recommended URF in IRIS[5] (0.23), result = 0.0054; and
- finding the ratio of the two risk estimates: 1.1.

As can be seen in the two columns of Table III presenting risks for the two PCME metrics, including fibers between 0.25 and 0.4 μm (in the N-PCME metric) can increase risk estimates relative to risks estimated using I-PCME (which excludes these fibers) by a factor of up to four.

Excluding UICC Anthophyllite, risks estimated for all other dusts in Table III using the thin and all-widths metrics (the last two columns each under chrysotile and amphibole in the table) are entirely consistent[11]; they vary by less than a factor of two from one another for the same dust. Similar consistency is also seen when comparing risks from these two metrics across the 10 size distributions used in the 2008 analysis[4]. This is accomplished (for amphiboles) by multiplying the fraction of amphiboles (Table 3[4]) by the size fraction representing each metric (Table 2[4]) and applying the corresponding URF from Table II of this study (data not shown). Thus, for only one of 23 independent distributions evaluated here (10 from 2008[4] and 13 from Table II) are risks derived from these two metrics not consistent and this is significant (p = 0.043), which suggests something special about the anthophyllite. Implications of this finding are considered further in the Discussion Section.

As the dimensions of fibers included in the thin and all-widths metrics differ more radically from one another (w ≤ 0.4 vs. ≤ 3 μm) than the earlier Berman and Crump metrics included in Table II, it is not surprising that (again ignoring anthophyllite) risks estimated using the earlier metrics are also consistent with each other and with those estimated using the 2008[4] metrics; amphibole risks estimated across all these protocols vary by less than a factor of three for the same dust and chrysotile risks vary by, at most, slightly more than six. That the risk estimates from the 2003 study[3] tend to be slightly larger than those from the 2008 study[4] simply reflects the informal (non-statistical) and highly conservative manner in which recommended upper bounds were derived in the 2003 study compared to use of statistically estimated UCB's in the 2008 study.

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10 As indicated in the Berman and Crump protocols[2-4], the conservative values are the recommended values. Moreover, this author has consistently used these conservative values when applying these protocols at environmental sites to assess risk (see references in Table 4).

11 Remembering that consistency cannot be judged without addressing uncertainty, confidence intervals (CIs) for the normalized risks presented in Table III can be estimated by considering: (1) they would be no smaller than the CIs of the corresponding URF from which each normalized risk is derived and (2) that the CIs for the corresponding URFs can be approximated as twice the interval between the best and upper bound estimates presented for these URFs in Table II. Thus, amphibole risks estimated using Berman and Crump protocols that vary by less than a factor of four can be considered consistent. Similarly, chrysotile risks that vary by a factor of six or less can be considered consistent.

Unfortunately, evaluating consistency between risks estimated using either PCME metric and the Berman and Crump metrics is difficult to assess because, for amphiboles, the estimated uncertainty interval is larger for IRIS than for Berman and Crump (Table II) while, for chrysotile, uncertainty cannot reasonably be defined for IRIS because the URF for chrysotile was extrapolated from amphibole data and the uncertainty of the extrapolation is undefined.

The fact that some of the normalized risks derived for chrysotile dusts using the Berman and Crump metrics are larger than one and some less than one indicates that neither the IRIS[5] nor the Berman and Crump protocol[2-4] is uniformly more health protective than the other toward chrysotile; the normalized risk depends on the specific characteristics of each dust. By definition, applying the IRIS protocol using N-PCME (rather than I-PCME) may be somewhat more conservative for chrysotile, although it is not clear that such added protection is in fact necessary (see discussion of reliability below). In contrast, with regard to amphibole asbestos, the risks estimated using the Berman and Crump protocol[4] for many of these dusts are more than 10 times that indicated for I-PCME with long amosite exhibiting risks that are even larger. Thus, it appears that the Berman and Crump protocol may be substantially more health protective than IRIS when amphibole asbestos exposures are involved and this may be important (see reliability discussion below).

Table IV presents the mean and range of normalized risks observed across the set of samples analyzed from the series of sites indicated in the table. In this case, the table presents the risks estimated using the Berman and Crump (2001) protocol[2] normalized to risks estimated using the IRIS protocol[5] paired with the *N-PCME* metric[12]. As can be seen in the table, the range of normalized risks estimated using the Berman and Crump protocol for chrysotile are close to one but vary up to a factor of two, meaning that they are approximately similar to (or just slightly larger than) those estimated using the N-PCME metric. This suggests, among other things, that chrysotile at these sites may be somewhat longer and thinner than found in the entire set of samples evaluated in 1995[38] (Table III) because the 2001 protocol[2] metric, by definition, is dominated by fibers that are longer and thinner than those counted for the N-PCME metric and risks estimated using the 2001 metric are similar to or larger than those derived using the IRIS protocol with the N-PCME metric in Table IV, but smaller in Table III. It also suggests that (in at least some environments) the IRIS[5] protocol coupled with I-PCME may somewhat underestimate risks even in chrysotile environments. This is because, as I-PCME fibers are subsets of N-PCME fibers, I-PCME risk estimates are necessarily smaller than N-PCME risk estimates. Any such effects, however, are apparently small and may be unimportant.

Regarding exposures to amphibole asbestos, (with one exception) Table IV suggests that risks estimated using the 2001 thin metric[2] are between approximately 5 and 100 times larger than those estimated using the N-PCME metric (with averages that vary between approximately 10 and 50 times). Coupled with observations from Table III, indicating that the N-PCME metric provides risk estimates that are up to four times larger than the I-PCME metric, while amphibole risks estimated using the 2001[2] and the 2008[4]-thin metrics are approximately equal, this suggests that (if appropriate data became available) application of the 2008-thin or all-widths metrics (from the newest version of the Berman and Crump protocol) at the sites listed in Table IV should generally result in estimated risks to amphibole asbestos that are substantially more than an order of magnitude larger than those estimated using the IRIS protocol. In fact, even if one were to discount these by a factor of two or three (which represent the

[12] Risks could not be estimated for other metrics because data from these studies would not generally support it.

ratios of UCB's to best estimates, Table II), it appears that (even using best estimates) the current IRIS protocol may still underestimate risk (relative to Berman and Crump 2008) for amphibole asbestos by at least an order of magnitude in most environments and, in some environments, by substantially more.

The one exception in Table IV is interesting. This is a school site in El Dorado County, California studied by the EPA[50]. That application of the 2001[2] metric at this site results in a risk estimate that is less than that obtained by applying the N-PCME metric, suggests that something is unique about the amphiboles analyzed at this site.[13] Although additional work would be needed to evaluate any conjectures, the leading candidate explanation is that the amphiboles at this site may not be true asbestos, but a form of massive amphibole[51]. Data show they are substantially thicker than those observed in the other environments reported here[50], but whether this means that they are something other than amphibole asbestos remains to be confirmed. It is known that amphibole asbestos is ubiquitous in El Dorado County[52,53], but this does not mean that every occurrence of amphibole in the County is necessarily asbestos or even contains asbestos.

If one considers that amphibole risks estimated (as described above) for the epidemiology studies of the 2008 meta analysis[4] are all larger than those estimated using IRIS and N-PCME, than the exception in Table IV represents one out of 22 independent tests (including 10 distributions from the meta analysis[4], the seven amphibole distributions from Table III, and the five amphibole distributions from Table IV), which is significant ($p = 0.045$). It can therefore be said that the IRIS protocol significantly underestimates amphibole risk relative to the Berman and Crump protocol.

4.3. Evaluating Reliability

Implications regarding the fitting of various protocols to study-specific K_M's and K_L's are separately addressed below.

4.3.1. *Regarding study-specific K_M's*

Figure 1 is a plot comparing predicted study-specific K_M's (estimated using various risk protocols) to the K_M's calculated from the epidemiology studies themselves (Table I, based on the evaluation described in Table 4 of Berman and Crump[7])[14]. The vertical bars in the figure depict the uncertainty bounds for the study-specific K_M's derived directly from the individual epidemiology studies.

The IRIS protocol[5] assigns the same potency to all studies and the horizontal line near the center of Figure 1 represents this value (using the N-PCME metric[4]). As indicated in the 2008 study[4] and can be seen in the figure, the IRIS protocol provides a poor fit to the data as the IRIS estimate falls outside of the uncertainty bounds indicated for several of the individual studies: Quebec chrysotile mining, South Carolina textile manufacturing, Ontario asbestos-cement manufacturing, and Wittinoom crocidolite mining.

Because the I-PCME metric is a subset of the N-PCME metric, risks estimated using the I-PCME metric will be smaller in all environments than risks estimated using the N-PCME metric. I-PCME risks are depicted in Figure 1 as small, shaded circles (all below the horizontal line in the figure). As can be seen

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13 In fact, this is the only set of samples involving exposure to amphiboles of which the author is aware in which the Berman and Crump protocol[2-4] provides a smaller risk estimate than the IRIS protocol.

14 While this figure is similar in appearance to Figure 1[4], a different set of exposure metrics are depicted.

in the Figure, use of the I-PCME metric provides no improvement in fit to the data; it generally worsens the fit to amphibole asbestos and mixed fiber exposures while only slightly improving the fit to chrysotile exposures.

In contrast, the "thin" (10 μm < L, w < 0.4 μm) and "all-widths" (10 μm < L) metrics[4] (X's and open circles) can be seen in Figure 1 to provide substantially better fits as their predicted values fall within or at the edge of the uncertainty bounds for all studies in the figure, except that for Quebec chrysotile mining. In general therefore, risk estimates derived using the Berman and Crump protocol[4] should be considered more reliable, at least toward mesothelioma.

K_M's estimated from the informal model used to calculate K_M/K_L ratios in the 1986 Update[6] are also depicted in Figure 1 (shaded triangles). As can be seen in the figure, while agreement between study-specific K_M's and K_M's estimated using this model is reasonably good for mixed exposures, K_M's for predominantly chrysotile exposures are substantially overestimated by this model. Implications are further addressed in the Discussion Section.

The shaded squares in Figure 1 represent a metric with L>20 μm and w<1.5 μm, which was recently identified[18] as a candidate for better predicting lung cancer and mesothelioma risk than the metrics discussed heretofore. As can be seen in the figure, for the four environments from which suitable values for this metric can be estimated, it provides the best overall agreement with the study-specific K_M's. Such results should still be considered preliminary, however, because available data are not yet sufficient to test this metric over a broad enough range of epidemiology studies to demonstrate its general validity. Nevertheless, work toward reconstructing the relevant, historical exposures is recommended and is progressing, given the promise suggested for this and other candidate metrics under consideration. Among other things, for example, virtually the same improvement is noted whether the width of this metric is restricted to 0.4 μm or expanded to include all widths (data not shown). Thus, the breadth of studies to which current data will allow application of this metric is too sparse to allow adequate exploration of the effects of fiber width.

4.3.2. *Regarding study-specific K_L's*

Figure 2 is a plot comparing predicted study-specific K_L's (estimated using various risk protocols) to the K_L's calculated from the epidemiology studies themselves (Table I[7], based on the evaluation described in Table 3[7]). It is identical in construction and interpretation to Figure 1 and (with one exception) presents fits associated with the same metrics; the informal model from the 1986 update[6] is missing from this figure because it does not provide estimates for K_L.

As in Figure 1, the IRIS protocol[5] coupled with N-PCME provides a poor fit to the lung cancer data in Figure 2. This metric overestimates the observed potencies for Quebec chrysotile mines and mills and underestimates the potencies for both the South Carolina textile plant and the Paterson, NJ insulation plant. Based on the locations of the small, shaded circles in the Figure, the I-PCME metric does no better. Unlike Figure 1, however, fits for lung cancer by either the thin or all-widths metric[4] are improved only marginally over the PCME metrics, as neither of these metrics adequately reconciles the disparity between the South Carolina and Quebec studies either. Still, the marginal improvement for lung cancer combined with the substantial improvement for mesothelioma indicates that, overall, the Berman and Crump protocol[4] should be considered more reliable for predicting asbestos-related cancer risk than the IRIS protocol[5]. Moreover, as the thin and all-widths metrics are each seen to fall within the uncertainty bounds for all of the amphibole and mixed exposure environments in both figures (i.e.,

fitting both K_M's and K_L's), the Berman and Crump protocol[4] should be considered more reliable especially for amphibole asbestos.

Interestingly, the metric incorporating fibers with 20 μm < L and W < 1.5 μm[18], the shaded squares in Figure 2, appears to reconcile the Quebec and South Carolina studies; the squares fall within or at the edge of the uncertainty bounds for both studies. Thus, this metric holds promise. However, until additional data are developed that will allow this metric to be fit to a larger number of studies, whether this or a closely-related metric will ultimately prove to provide complete reconciliation of the available epidemiology data remains to be determined.

5. DISCUSSION

It was not unreasonable for Nicholson to assume that chrysotile and amphibole asbestos are equally potent toward the induction of mesothelioma given: (1) the lack of available K_M values from cohorts exposed predominantly to chrysotile, (2) the generally similar K_M/K_L ratios determined for both chrysotile and amphibole using his informal model[6], and (3) the apparent agreement between the results from this model and the four K_M's (from amphibole or mixed-asbestos environments) available to Nicholson[6]. However, when the results from the informal model are fit (using Equation 2) against the broader range of study-specific K_M's available today, even this model shows a significant difference in mesothelioma potencies between chrysotile and amphibole, as the model overestimates values for chrysotile (Figure 1).

When size is also considered, the relative potency of chrysotile (rpc) from Equation 2 is found to be significantly different from one for both the thin[4] and all-widths[4] metrics ($p = 0.025$ and 0.01, respectively). Even when size is restricted to the PCME metric, rpc is just significantly different from one ($p = 0.053$). Also as expected, in no case was the ratio Q from Equation 2 found to be significantly different from one. Thus, consistent with both the Berman and Crump studies[2-4] and Hodgson and Darnton[1], even the 1986 update[6] should now be considered to support the conclusion that amphibole asbestos is significantly more potent toward the induction of mesothelioma than chrysotile. Moreover, a lower-bound estimate of the potency difference can be defined, which is based on the sensitivity analysis reported in Berman and Crump[4]; amphibole asbestos is at least 200 times more potent toward mesothelioma than chrysotile.

Given the above, reconciliation of the IRIS[5] and Berman and Crump protocols[4] is considered separately for chrysotile and amphibole asbestos. Regarding amphibole, the IRIS protocol significantly underestimates risks posed by amphibole exposure and such underestimation may substantially exceed a factor of 10 in at least some environments. Moreover, given that the Berman and Crump protocol is more reliable overall and especially for amphiboles, the underestimation of amphibole risk should be considered important.

Aside from study to study variation (which appears to be driven primarily by differences in fiber size), the general, order of magnitude difference in risk estimates derived for amphiboles that are respectively obtained using the IRIS[5] and Berman and Crump[4] protocols is almost entirely attributable to the selection of the particular K_M's used to develop the corresponding URFs. If Nicholson (or IRIS) had selected either the maximum values or a reasonable upper bound estimate of the mean of the values reported in the 1986 update[6] (instead of the lowest of the observed K_M's), risks estimated for amphiboles using IRIS would be about an order of magnitude larger (Table II). This would bring them, on average, into better agreement with risks estimated using Berman and Crump. However, the Berman

and Crump protocol is also more reliable at predicting risk across individual environments because it addresses the effects of fiber size.

Regarding chrysotile, risks estimated using the two protocols may vary by up to an order of magnitude from one another (with differences going in either direction), depending on the size characteristics of the fibers in any particular environment. However, because the logic used to support the assumption that chrysotile and amphibole asbestos are equipotent toward the induction of mesothelioma[6] was shown to be in error (see above), it appears that the IRIS protocol may be overestimating chrysotile risks rather than the Berman and Crump protocol underestimating such risks. Moreover, at least based on results from the available environmental studies (Table IV), chrysotile risks derived using both protocols are in substantial agreement. Nevertheless, perhaps until a metric can be identified that entirely reconciles chrysotile epidemiology, chrysotile risks should be estimated using both IRIS and Berman and Crump with emphasis placed on the more conservative of the corresponding risk estimates. In fact, a metric that reconciles chrysotile epidemiology may already have been identified[18] (as suggested by Figures 1 and 2), although more data are needed to fully evaluate its performance.

Previously published studies[61, 62] of women living in the mining areas of Quebec also report that the IRIS protocol overestimates lung cancer and mesothelioma risks attributable to (predominantly) chrysotile exposure and their findings are quantitatively consistent with those reported herein. In those studies, lung cancer and mesothelioma risks estimated using IRIS are respectively reported to be overestimated by >10X and 10 to 250X, which are consistent with the 12X and 40X indicated in Figures 2 and 1, respectively, for the Quebec cohort of miners and millers in this study. In contrast, risks estimated for this cohort using the new metric proposed herein (which addresses contributions from the amphibole component of these exposures) are entirely consistent with the cohort-specific risks shown in these figures as well as those from the earlier studies.[61,62] After adjusting for differences in populations at risk, the approximately 3X greater potency observed in Thetford Mines vs. Asbestos, Quebec in these earlier studies is also consistent with the 2X greater mesothelioma potency reported in our 2008 study.[7]

The order of magnitude risk difference observed between the 2008 thin and all-widths metrics[4] applied to UICC Anthophyllite (Table III) reflects the fact that this dust contains relatively thick fibers (Appendix, Table A-II) and suggests that inclusion of this dust in a future meta analysis would increase the statistical power with which the effects of various size metrics might be distinguished (particularly with regard to width), if a health effects study of such material could be found or would be newly implemented. This would add to the set of epidemiology studies for which historical exposures are being reconstructed so that the reliability of newer metrics can be evaluated.

6. CONCLUSIONS

The IRIS[5] and Berman and Crump[2-4] protocols for predicting asbestos-related cancer risks can be reconciled. At the same time, the IRIS protocol may substantially underestimate risk when exposure is primarily to amphibole asbestos, due primarily to arbitrary selection of the lowest of available K_M's as an input to the protocol. Because the Berman and Crump protocol uniquely addresses the effects of fiber size and K_L's and K_M's were selected based on fitting of the available data, environment-specific risk predictions by this protocol are more reliable overall and this is particularly true for amphibole asbestos exposures. Although chrysotile epidemiology has not yet been entirely reconciled by either protocol, a new metric has recently been identified[18] that appears to achieve such reconciliation. Nevertheless,

additional data and more study are required before the performance of this new metric (and an associated protocol) can be validated.

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DECLARATION OF INTERESTS

I consult for a variety of government and private organizations with competing interests, none of whom are involved in this work. Funding provided for writing this manuscript and conducting the supporting analyses was provided as a grant; the sponsor (the National Stone, Sand, and Gravel Association) had no input into the work.

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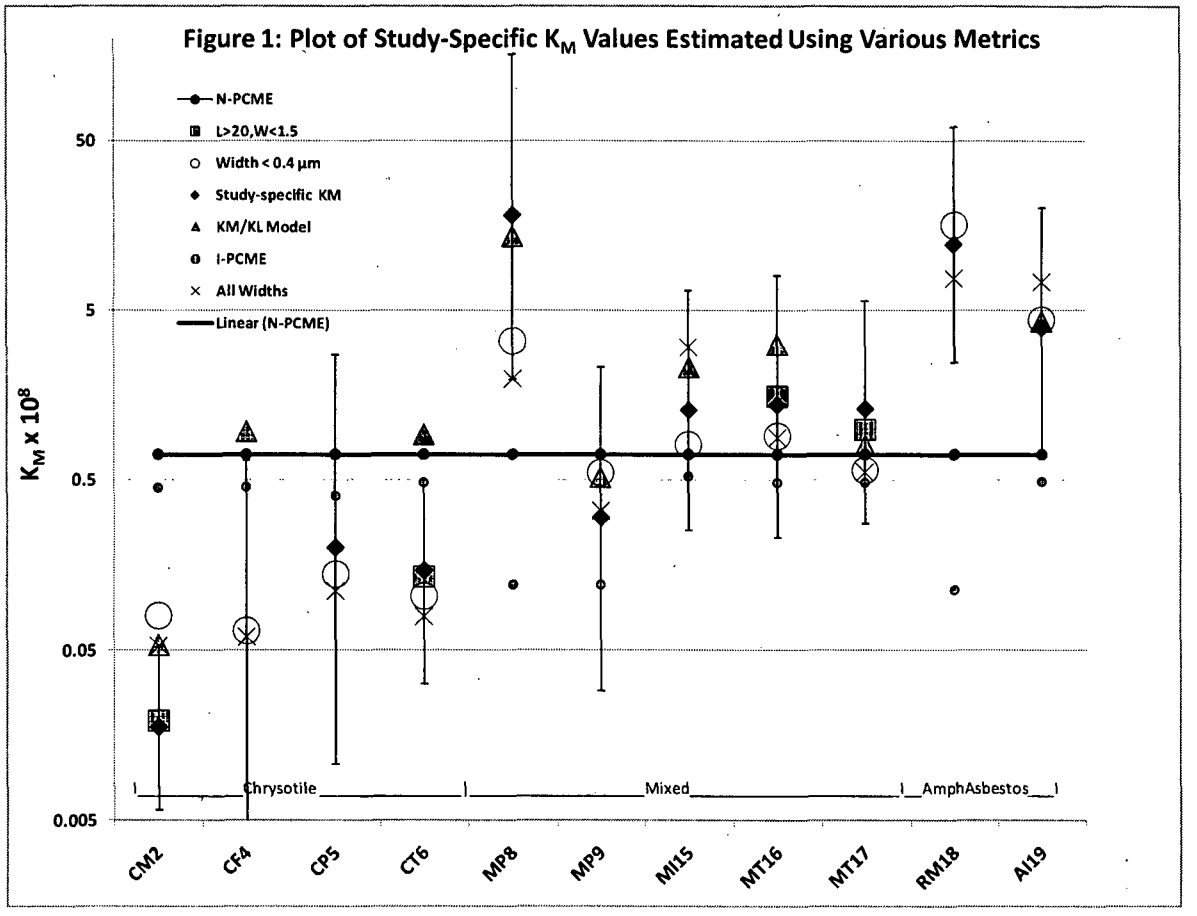
FIGURES

Figure 1: Plot of Study-Specific K_M Values Estimated Using Various Metrics



Key:

Code at bottom indicates specific study environments.

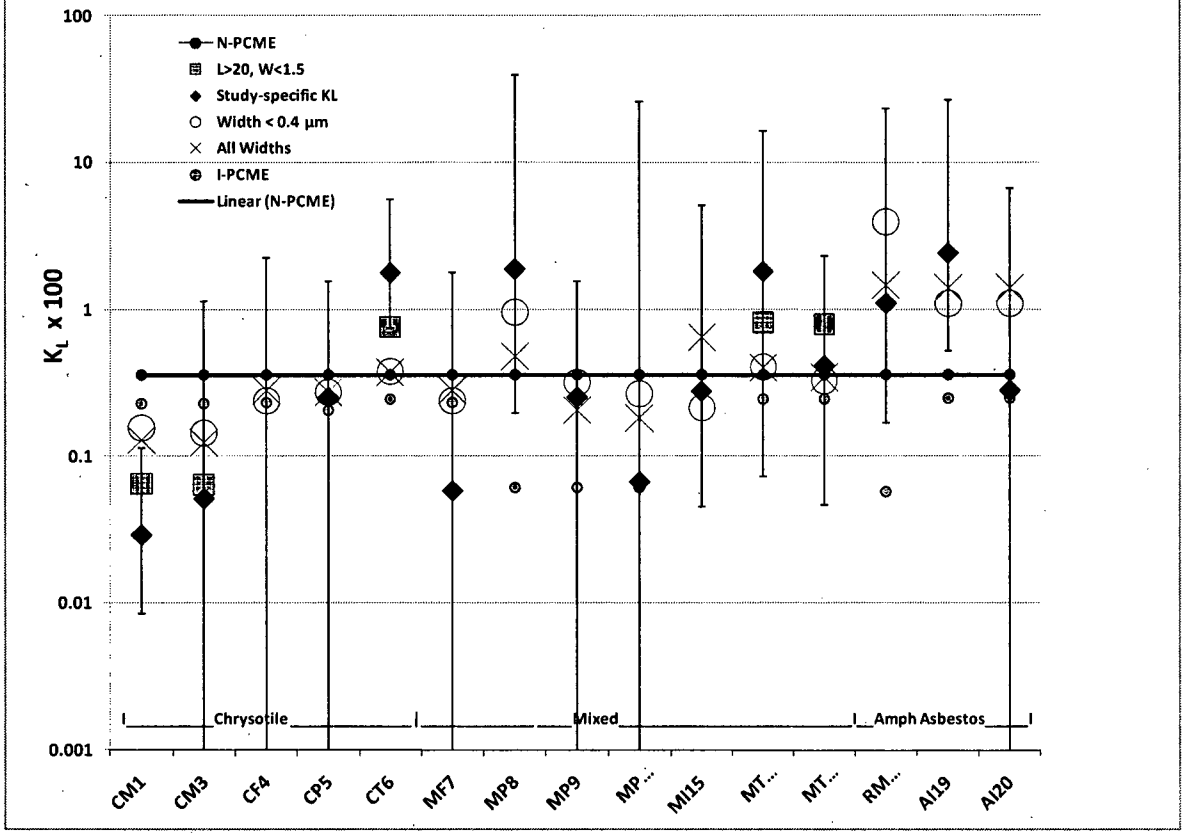
First digit (predominant fiber type): A=amosite, C=chrysotile, M=mixed fiber, R=crocidolite, T=winchite-richterite

Second digit (study environment): F=friction product manufacturing, I=insulation manufacturing, M=mining, P=ac pipe manufacturing, T=textile manufacturing, O=miscellaneous manufacturing

Last two digits (study cohorts): 2=Quebec mines, 4=Connecticut friction product workers, 5=New Orleans ac pipe manufacturers, 6=South Carolina textile manufacturers, 8=Ontario ac pipe manufacturers, 9=New Orleans ac pipe manufacturers, 15=Insulation appliers, 16=Pennsylvania textile workers, 17=British textile workers, 18=Australian crocidolite miners, 19=New Jersey insulation manufacturers.

Source: Berman and Crump[4], Figure 1.

Figure 2: Plot of Study-Specific K_L Values Estimated for Various Metrics



Key:

Code at bottom indicates specific study environments:

First digit (predominant fiber type): A=amosite, C=chrysotile, M=mixed fiber, R=crocidolite, T=winchite-richterite

Second digit (study environment): F=friction product manufacturing, I=insulation manufacturing, M=mining, P=ac pipe manufacturing, T=textile manufacturing, O=miscellaneous manufacturing

Last two digits (study cohorts): 1=Quebec mines,3=Italian miners, 4=Connecticut friction product workers, 5=New Orleans ac pipe manufacturers, 6=South Carolina textile manufacturers, 7=British friction product manufacturers, 8=Ontario ac pipe manufacturers, 9=New Orleans ac pipe manufacturers, 10=Swedish ac pipe manufacturers, 15=Insulation appliers, 16=Pennsylvania textile workers, 17=British textile workers, 18=Australian crocidolite miners, 19=New Jersey insulation manufacturers, 20=Texas insulation manufacturers.

Source: Berman and Crump[4], Figure 2.

TABLES

TABLE I: SUMMARY OF POTENCY FACTORS (K_L'S AND K_M'S) DETERMINED, RESPECTIVELY, FROM BERMAN AND CRUMP (2008a)[4] AND THE 1986 UPDATE[6]

	Predominantly Chrysotile				Mixed Exposures				Predominantly Amphibole Asbestos			
Industry	1986 Update[6]	Berman and Crump[4]	1986 Update[6]	Berman and Crump[4]	1986 Update[6]	Berman and Crump[4]	1986 Update[6]	Berman and Crump[4]	1986 Update[6]	Berman and Crump[4]	1986 Update[6]	Berman and Crump[4]
Location	K_L x 100	K_L x100	K_M x10^8	K_M x10^8	K_L x100	K_L x100	K_M x10^8	K_M x10^8	K_L x100	K_L x100	K_M x10^8	K_M x10^8
Mining and Milling												
Quebec	0.06	0.029		*0.012* [1]								
				0.021 [2]								
	0.17											
Italy	0.081	0.051										
Wittenoom										1.1		*12*
Libby										0.26		
										0.36		
Friction Products												
Connecticut	0.01	0		*0*								
Britian					0.058	0.058						
Asbestos Cement												
New Orleans		0.25		*0.2*	0.53	0.25		*0.3*				,
Ontario					4.8	1.9	*12*	*18*				
Sweden						0.067						
Belgium						0.0068						
Textile Production												
South Carolina	2.8	1.8		*0.15*								
	2.5	1		*0.088*								
Pennsylvania					1.4	1.8		*1.4*				
Rochdale					1.1	0.41	*1*	*1.3*				
Insulation Manufacture												
Patterson									4.3	2.4	*3.2*	*3.9*
Tyler										0.28		
Factory Retirees					0.49	0.11						
Insulation Application					0.75	0.28	*1.5*	*1.3*				

Notes: Citations for the original epidemiology studies from which these potency factors are estimated are provided in Berman and Crump (2008a)[4].

[1] Specific to the mine in Asbestos, Quebec

[2] Specific to the mines in Thetford Mines, Quebec

TABLE II: CANCER UNIT RISK FACTORS ESTIMATED IN THE 1986 UPDATE[6], IN IRIS[5], AND BY BERMAN AND CRUMP[2-4] USING ORIGINAL AND RECONCILED U.S. MORTALITY AND SMOKING DATA

	Chrysotile				Amphiboles			
Mortality/Smoking Scenario:[1]	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Source of potency factors:								
Risk Protocols for PCME Metric[2]								
IRIS[5]	0.23	0.35		0.31	0.23	0.35		0.31
1986 Update[6]								
Best estimate[3]						0.35		0.31
UCB[4]								1.28
Recommended Upper Bound[5]								5.04
Based on Maximum K_L and K_M								2.88
Risk Protocol for "Protocol Structures"[6]								
Berman and Crump 2001[2]								
Best estimate			0.08	0.10			5.53	5.82
Recommended Upper Bound[5]			0.28	0.34			9.87	10.48
Risk Protocol for "Long Protocol Structures" that are also thin[7]								
Berman and Crump 2003[3]								
Best estimate				0.07				5.67
Recommended Upper Bound[5]				0.62				19.94
Berman and Crump 2008[4]								
Best Estimate				0.05				6.31
UCB[4] *(Recommended)*				0.21				13.80
Risk Protocol for "Long Protocol Structures" that include all widths[8]								
Berman and Crump 2008[4]								
Best Estimate				0.03				2.75
UCB[4] *(Recommended)*				0.10				5.75

Notes:

[1] **Scenario 1**: Used U.S. Mortality statistics for 1977[54], Smoking mortality statistics[55], Smoking rate estimates[6], converted to lifetime-continuous exposure based on inhaled volume[6].

Scenario 2: Used U.S. Mortality statistics for 1977[54], Smoking mortality statistics from Hammond[55], Smoking rate estimates[6], converted to lifetime-continuous exposure based on fraction of week worked.

Scenario 3: Used U.S. Mortality statistics for 1980, Smoking mortality statistics from Hammond[55], Smoking rate estimates[6], converted to lifetime-continuous exposure based on fraction of week worked.

Scenario 4: Used U.S. Mortality statistics for 2000[56], Smoking mortality statistics[57,58], Smoking rate estimates[59], converted to lifetime-continuous exposure based on fraction of week worked.

[2] N-PCME: 5 μm < L, 0.25 μm < w, 3 < AR; I-PCME: 5 μm < L, 0.4 μm < w, 3 < AR; although I-PCME is most directly relevant here, both PCME metrics are presented because they have each been paired with the IRIS-derived slope factors in this and other studies.

[3] In this case only, "best estimate" is the estimate arbitrarily defined by the study author, not a statistically determined best estimate.

[4] In this study, upper confidence bounds (UCB's) for unit risk factors were derived from the indicated lifetable analysis by inputting UCB values for K_L and K_M determined as described in Berman and Crump 2008a[4] by fitting the corresponding sets of K_{Lj} and K_{Mj} values cited in the indicated protocol.

[5] Recommended upper bounds for unit risk factors are the upper bound values that were informally estimated (i.e., not based on any formal statistical calculation or fit of data) by study authors, which are provided in the indicated protocols.

[6] 0.003*(5 μm < L, w < 0.5 μm) + 0.997*(10 μm < L, w < 0.5 μm)

[7] 10 μm < L, w < 0.4 μm

[8] 10 μm < L, w < 3.0 μm

TABLE III: RISK FROM EXPOSURE TO INDICATED MATERIAL ESTIMATED USING INDICATED PROTOCOL AND NORMALIZED TO RISK ESTIMATED USING IRIS AND THE I-PCME METRIC

	IRIS		Berman and Crump							
			Chrysotile				Amphibole			
Dust Type	N-PCME	I-PCME	2001 Thin	2003 Thin	2008 Thin	2008 All W	2001 Thin	2003 Thin	2008 Thin	2008 All W
Short Amosite	1.5	1.0					11	20	9.4	7.6
Long Amosite	2.0	1.0					35	66	35	28
Factory Amosite	1.5	1.0					8.3	15	6.3	7.1
UICC Amosite	1.9	1.0					11	20	10	12
Factory Chrysotile	1.5	1.0	0.4	0.7	0.2	0.1				
Short Chrysotile	3.0	1.0	2.1	3.7	1.1	0.6				
WDC Chrysotile	1.9	1.0	1.7	3.0	0.7	0.7				
UICC-B Chrysotile	4.0	1.0	0.9	1.6	0.5	0.3				
UICC-A Chrysotile	2.9	1.0	1.2	2.2	0.6	0.4				
Long Chrysotile	1.6	1.0	0.3	0.5	0.1	0.1				
Korean Tremolite	1.2	1.0					8.2	15	6.1	12
UICC Crocidolite	1.5	1.0					9.2	17	8.3	11
UICC Anthophyllite	1.1	1.0					2.9	5.4	1.1	10

Data Source: Appendix

TABLE IV: COMPARISON OF APPROACHES FOR EVALUATING ASBESTOS-RELATED RISKS APPLIED AT SELECTED SITES

	Diamond XX[44]	Waukegan[45]	Southdown[46]	Libby[47]	Klamath Falls[48,49]	El Dorado[50]
Year of Study	1994	2002	2003	2003	2005	2005
Source of Asbestos	Natural	Product Debris	Natural	Natural	Product Debris	Natural
Risk Relative to PCME						
N-PCME	1	1	1	1	1	1
Berman and Crump[2]						
Chrysotile	(1.2x)	0.3 to 2x (0.9x)			1.0 - 1.2x (1.1x)	
Amphibole		4 to 100x (50x)	15 - 90x	5.9 - 7.5x	12 - 50x (30x)	(0.04)

APPENDIX

Bi-variate size distributions are presented in two tables for fibers and bundles observed in dusts generated from the dusts studied by Davis and coworkers[31-37] and the UICC samples[39-43, 60] that were analyzed to support a meta analysis of the animal inhalation studies[38]. The manner in which the dusts were generated and analyzed was previously described[38]. As results of these analyses were not previously published, however, they are presented here.

Table A-I provides the fraction of primary fibers and bundles for each of the indicated size categories in dusts from the samples listed. Table A-II provides the fractions of primary and component fibers and bundles.

TABLE A-I: FRACTION OF INDICATED SIZES IN DISTRIBUTION OF PRIMARY FIBERS AND BUNDLES OF DUSTS FROM INDICATED FIBER TYPE

	Length<5					5<Length<10					10<Length<20					20<Length				
Fiber Type	Width <0.25	0.25< Width <0.4	0.4< Width <0.5	0.5< Width <1.5	1.5< Width	Width <0.25	0.25< Width <0.4	0.4< Width <0.5	0.5< Width <1.5	1.5< Width	Width <0.25	0.25< Width <0.4	0.4< Width <0.5	0.5< Width <1.5	1.5< Width	Width <0.25	0.25< Width <0.4	0.4< Width <0.5	0.5< Width <1.5	1.5< Width
SHORT AMOSITE	0.6134	0.2328	0.0703	0.0315	0.0000	0.0108	0.0065	0.0082	0.0135	0.0000	0.0009	0.0052	0.0030	0.0026	0.0000	0.0000	0.0000	0.0004	0.0009	0.0000
LONG AMOSITE	0.2473	0.1563	0.0380	0.0229	0.0000	0.0894	0.1224	0.0322	0.0694	0.0000	0.0208	0.0624	0.0318	0.0624	0.0000	0.0065	0.0269	0.0024	0.0086	0.0000
FACTORY AMOSITE	0.4440	0.2010	0.0652	0.0455	0.0000	0.0245	0.0600	0.0524	0.0715	0.0061	0.0061	0.0055	0.0055	0.0102	0.0014	0.0000	0.0000	0.0014	0.0000	0.0000
UICC AMOSITE	0.2901	0.1939	0.0877	0.0691	0.0000	0.0388	0.1113	0.0523	0.0860	0.0000	0.0000	0.0152	0.0034	0.0472	0.0000	0.0000	0.0017	0.0017	0.0017	0.0000
FACTORY CHRYSOTILE	0.6879	0.0850	0.0260	0.0630	0.0052	0.0249	0.0295	0.0116	0.0306	0.0162	0.0075	0.0052	0.0012	0.0035	0.0000	0.0000	0.0012	0.0006	0.0006	0.0006
SHORT CHRYSOTILE	0.7981	0.0636	0.0116	0.0173	0.0000	0.0317	0.0266	0.0134	0.0032	0.0005	0.0076	0.0204	0.0019	0.0005	0.0009	0.0000	0.0014	0.0014	0.0000	0.0000
WDC CHRYSOTILE	0.4231	0.0520	0.0000	0.0416	0.0000	0.0988	0.0613	0.0146	0.0146	0.0000	0.0333	0.0644	0.0229	0.0249	0.0000	0.0198	0.0218	0.0239	0.0780	0.0052
UICC-B CHRYSOTILE	0.5620	0.2350	0.0434	0.0244	0.0000	0.0463	0.0546	0.0135	0.0081	0.0000	0.0005	0.0062	0.0005	0.0049	0.0000	0.0000	0.0005	0.0000	0.0000	0.0000
UICC-A CHRYSOTILE	0.5803	0.1916	0.0980	0.0315	0.0000	0.0282	0.0382	0.0056	0.0091	0.0000	0.0025	0.0051	0.0047	0.0036	0.0006	0.0000	0.0000	0.0006	0.0006	0.0000
LONG CHRYSOTILE	0.7186	0.0570	0.0380	0.0323	0.0000	0.0368	0.0317	0.0272	0.0437	0.0000	0.0032	0.0025	0.0032	0.0051	0.0000	0.0000	0.0006	0.0000	0.0000	0.0000
KOREAN TREMOLITE	0.1407	0.0867	0.0730	0.0834	0.0000	0.0322	0.0744	0.0952	0.2236	0.0085	0.0085	0.0218	0.0185	0.0843	0.0204	0.0000	0.0085	0.0085	0.0085	0.0033
UICC CROCIDOLITE	0.4633	0.1404	0.1010	0.0281	0.0000	0.0582	0.0522	0.1024	0.0295	0.0000	0.0000	0.0000	0.0000	0.0054	0.0000	0.0000	0.0027	0.0000	0.0167	0.0000
UICC ANTHOPHYLLITE	0.1844	0.0641	0.0481	0.0699	0.0000	0.0000	0.0470	0.0550	0.3265	0.0195	0.0000	0.0000	0.0000	0.0779	0.0607	0.0000	0.0000	0.0000	0.0332	0.0137

Source: Study described in Berman et al.[38]

TABLE A-II: FRACTION OF INDICATED SIZES IN DISTRIBUTION OF PRIMARY AND COMPONENT FIBERS AND BUNDLES OF DUSTS FROM INDICATED FIBER TYPE

	Length<5					5<Length<10					10<Length<20					20<Length				
Fiber Type	Width <0.25	0.25< Width <0.4	0.4< Width <0.5	0.5< Width <1.5	1.5< Width	Width <0.25	0.25< Width <0.4	0.4< Width <0.5	0.5< Width <1.5	1.5< Width	Width <0.25	0.25< Width <0.4	0.4< Width <0.5	0.5< Width <1.5	1.5< Width	Width <0.25	0.25< Width <0.4	0.4< Width <0.5	0.5< Width <1.5	1.5< Width
SHORT AMOSITE	0.6924	0.1650	0.0719	0.0325	0.0000	0.0052	0.0078	0.0056	0.0128	0.0002	0.0004	0.0028	0.0014	0.0012	0.0000	0.0002	0.0000	0.0002	0.0004	0.0000
LONG AMOSITE	0.2625	0.1352	0.0312	0.0170	0.0000	0.0979	0.1152	0.0276	0.0697	0.0000	0.0294	0.0627	0.0352	0.0688	0.0000	0.0048	0.0279	0.0036	0.0112	0.0000
FACTORY AMOSITE	0.4334	0.2167	0.0519	0.0451	0.0000	0.0465	0.0631	0.0513	0.0524	0.0031	0.0061	0.0076	0.0055	0.0130	0.0007	0.0000	0.0000	0.0038	0.0000	0.0000
UICC AMOSITE	0.3727	0.1970	0.0606	0.0553	0.0000	0.0492	0.1038	0.0379	0.0598	0.0000	0.0015	0.0197	0.0068	0.0303	0.0000	0.0008	0.0015	0.0008	0.0023	0.0000
FACTORY CHRYSOTILE	0.6486	0.1003	0.0412	0.0623	0.0041	0.0316	0.0302	0.0101	0.0371	0.0137	0.0073	0.0055	0.0023	0.0032	0.0000	0.0000	0.0009	0.0005	0.0005	0.0005
SHORT CHRYSOTILE	0.7931	0.0702	0.0124	0.0124	0.0000	0.0329	0.0266	0.0147	0.0036	0.0003	0.0091	0.0188	0.0020	0.0010	0.0007	0.0003	0.0010	0.0010	0.0000	0.0000
WDC CHRYSOTILE	0.3602	0.0487	0.0028	0.0224	0.0000	0.1023	0.0755	0.0296	0.0168	0.0011	0.0386	0.0699	0.0252	0.0302	0.0000	0.0257	0.0397	0.0408	0.0621	0.0084
UICC-B CHRYSOTILE	0.5506	0.2157	0.0473	0.0210	0.0000	0.0563	0.0676	0.0129	0.0083	0.0000	0.0027	0.0107	0.0009	0.0047	0.0000	0.0000	0.0013	0.0000	0.0000	0.0000
UICC-A CHRYSOTILE	0.5929	0.1799	0.0733	0.0217	0.0000	0.0335	0.0476	0.0117	0.0092	0.0000	0.0050	0.0126	0.0059	0.0034	0.0002	0.0002	0.0015	0.0002	0.0010	0.0002
LONG CHRYSOTILE	0.6955	0.0636	0.0513	0.0243	0.0000	0.0480	0.0390	0.0261	0.0294	0.0000	0.0024	0.0036	0.0066	0.0045	0.0003	0.0000	0.0009	0.0009	0.0036	0.0000
KOREAN TREMOLITE	0.1634	0.0988	0.0665	0.0376	0.0000	0.0538	0.0668	0.1122	0.1738	0.0066	0.0093	0.0242	0.0292	0.1051	0.0131	0.0047	0.0093	0.0053	0.0179	0.0024
UICC CROCIDOLITE	0.5909	0.1300	0.0484	0.0183	0.0000	0.0431	0.0441	0.0467	0.0306	0.0000	0.0073	0.0039	0.0046	0.0130	0.0000	0.0000	0.0039	0.0020	0.0125	0.0007
UICC ANTHOPHYLLITE	0.1847	0.1105	0.0550	0.0577	0.0000	0.0107	0.0471	0.0687	0.2602	0.0060	0.0000	0.0047	0.0134	0.0925	0.0238	0.0000	0.0052	0.0093	0.0473	0.0033

Source: Study described in Berman et al.[38]